REMARKS

Following entry of the foregoing amendments, claims 1 to 3, 10, 11, 13 to 41, 44, 45, and 72 will be pending in this patent application. Claims 18, 19, 21 to 26, 30 to 35, 38 to 40, 44,45, and 72 have been withdrawn from consideration as drawn to non-elected subject matter. Claims 36 ad 37 have been amended herein. No new claims have been added, and no claims have been canceled.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Sequence Listing

The Office issued a notice to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures with the official action. In response to the notice, a sequence listing is being filed herewith, and the specification has been amended to insert the sequence listing and to incorporate sequence identification numbers. The amendments do not add new matter to the application.

Alleged Indefiniteness

Claims 36 and 37 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because sufficient antecedent basis for the phrase "the regulatory sequence-chromosomal gene fusion" allegedly does not exist. Without conceding the correctness of the assertion, and to advance prosecution, claims 36 and 37 have been amended to replace the cited phrase with the phrase "operably linked to a regulatory sequence," antecedent basis for which exists in claim 1, from which claims 36 and 37 depend. Support for the amendments is found throughout the specification as originally filed, and the amendment thus does not introduce new matter into the application. The rejection has been obviated, and applicants accordingly, respectfully, request withdrawal thereof.

Alleged Obviousness

Claims 1 to 3, 10, 11, 13 to 17, 20, 27 to 29, 36, 37, and 41 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by PCT patent application publication number WO 97/14805 ("the Morsey application"), Galen, *et al.*, *Infection and Immunity*, 1999, 67, 6424-6433 ("the Galen article"), and del Solar, *et al.*, *Microbiol. and Molec. Biol. Rev.*, 1998, 62, 434-464 ("the del Solar article") as evidenced by Hu, *et al.*, *Cell*, 1987, 48, 555-566 ("the Hu article"). Applicants respectfully request reconsideration and withdrawal of the rejection because the Patent Office has failed to establish that the claimed subject matter would have been obvious at the time of the invention.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims.[1] The Patent Office must also identify "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[2] In other words, the Office must identify "an apparent reason to combine the known elements *in the fashion claimed by the patent at issue*. To facilitate review, this analysis should be made explicit."[3]

The claims recite transformed host cells that comprise a chromosomal gene operably linked to a regulatory sequence. Expression of the chromosomal gene inhibits growth of the cells. The cells further comprise a plasmid having an origin of replication that encodes an antisense sequence that binds to mRNA transcribed from the regulatory sequence of the host cells, which inhibits the action of the chromosomal gene, permitting growth of the host cells. The claimed transformed host cells enhance antibiotic-free plasmid maintenance and selection, which improves plasmid yield and the concomitant yield of products encoded by the plasmids.

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[1] *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).
[2] *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, 1741.
[3] *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006).

Those of ordinary skill in the art would have had no reason to produce the claimed transformed host cells at the time of the invention in view of the teachings of the cited references. For example, the Morsey application describes a bacterial cell culture system in which a chromosome of the bacterial cells is irreversibly modified to produce a substance toxic to the cells. The bacterial cells contain a plasmid that produces a substance that inactivates the toxic substance. Specifically, the Morsey application describes a system containing a host cell chromosome that has been modified to contain the *hok* gene that encodes a toxic product, and a plasmid that has been modified to encode the *sok* gene. The Morsey application indicates that the transcripts of the *hok* and *sok* genes are antisense to one another and proposes that, when the plasmid is present, the *sok* gene transcript from the plasmid binds to the *hok* gene transcript transcribed from the chromosome, inhibiting the toxic effects of the *hok* gene product.[4] In the absence of the plasmid, the toxic *hok* gene product is expressed and the cells die.

The del Solar article is a review article that describes replication control mechanisms for circular bacterial plasmids and the role of antisense RNA in regulating replication and segregational stability of plasmids that occur *in nature*. The del Solar article teaches that all plasmid origins of replication produce transcribed RNA, and that some of this transcribed RNA, including RNAI, is used to control plasmid replication. The article explains that initiation of plasmid replication is primed by an RNA transcript known as RNAII and RNAI is complementary to a region in the 5' end of RNAII. Hybrid formation between RNAI and RNAII inhibits hybridization of the RNAII to DNA, thereby inhibiting the initiation of plasmid replication.[5]

Finally, the Hu article describes the *lac* operator-repressor system for regulating gene expression.

In contrast to the Office's assertion, those of ordinary skill in the art, armed with the teachings of the Morsey application and del Solar article, would have had no reason at the time of the invention to substitute the *hok/sok* system for the RNAI/RNAII system in order to develop

[4] Page 16, lines 18-26.
[5] Page 453, first column.

a method for plasmid maintenance. Significantly, the Morsey application does not propose a system in which a transcript from the *origin of replication* of a plasmid is antisense to the transcript of a regulatory sequence operably linked to a gene located on a host cell chromosome that inhibits cell growth. The *sok* gene is not and cannot be located at the origin of replication of the plasmid. Furthermore, the transcript from the plasmid *sok* gene binds directly to the transcript from the chromosomal toxic *hok* gene. The transcript of the *sok* gene does not bind to the transcript of a *regulatory sequence* operably linked to a gene that inhibits cell growth on the chromosome, as recited in the present claims. Moreover, in contrast to the RNA transcribed from the regulatory sequence of the presently claimed transformed host cells, both the RNAI and RNAII described in the del Solar article are encoded by *plasmids*. In addition, the del Solar article does not relate to improving plasmid maintenance and selection in cells in order to improve plasmid yield, nor does it suggest that pairs of RNA sequences known to be involved in plasmid regulation in nature could be exploited to allow plasmid maintenance and selection by moving one of the RNA sequences to the chromosome of a host cell.

Furthermore, those of ordinary skill in the art would have had no reason to utilize *lacI* as the chromosomally encoded repressor gene in the claimed transformed host cells. As discussed above, those of ordinary skill in the art would have had no reason before applicants' invention to combine the teachings of the Morsey application and the del Solar article, and those of ordinary skill in the art also would have had no reason to include the teachings of the Hu article in this combination.

Those of ordinary skill in the art would thus have had no reason to substitute the naturally occurring RNAI/RNAII system described in the del Solar article for the toxic *hok/sok* system used in the method of the Morsey application to arrive at the claimed transformed host cells. There is nothing in either the Morsey application nor the del Solar article to suggest that a system of plasmid maintenance employing the antisense properties of plasmid origins of replication would be particularly effective. In fact, the claimed transformed host cells display significant advantages over the *hok/sok* system described in the Morsey application. Unlike the *hok* gene product, antisense products encoded by the origin of replication of plasmids, such as those

recited in the claims, are not toxic to the host cell. Furthermore, the claimed transformed host cells can be used to maintain and select any plasmid containing an origin of replication regulated by an antisense sequence without the need for further modification of the plasmid. In practice, this means that the vast majority of plasmids that are commonly employed for therapeutic and cloning purposes can be maintained and selected in the claimed host cells without the need for *any* modification of the plasmids to introduce selectable markers. The complete avoidance of the need for any plasmid modification is clearly an advantage over prior art systems that necessitate the introduction of an antibiotic resistance gene into the plasmid, or the introduction of a *sok* gene (or deletion of a *hok* gene) in the plasmid, as required by the system described in the Morsey application.

The claimed transformed host cells enable plasmid maintenance and selection without the need for *any* plasmid modification. It would not have been obvious to those of ordinary skill in the art in view of the teachings of the cited references before applicants' invention that plasmids containing an origin of replication encoding a sequence antisense to mRNA transcribed from a regulatory sequence operably linked to a chromosomal gene that inhibits cell growth could be used for this purpose. The claimed transformed host cells therefore would not have been obvious in view of the cited art, and applicants according, respectfully, request withdrawal of the rejection.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the official action of record. An early and favorable action is accordingly, respectfully requested.

Respectfully submitted,

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/Jane E. Inglese/
Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439